Happy heart syndrome: role of positive emotional stress in takotsubo syndrome

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Abstract: AIMS: Takotsubo syndrome (TTS) is typically provoked by negative stressors such as grief, anger, or fear leading to the popular term 'broken heart syndrome'. However, the role of positive emotions triggering TTS remains unclear. The aim of the present study was to analyse the prevalence and characteristics of patients with TTS following pleasant events, which are distinct from the stressful or undesirable episodes commonly triggering TTS. METHODS AND RESULTS: Takotsubo syndrome patients with preceding pleasant events were compared to those with negative emotional triggers from the International Takotsubo Registry. Of 1750 TTS patients, we identified a total of 485 with a definite emotional trigger. Of these, 4.1% (n = 20) presented with pleasant preceding events and 95.9% (n = 465) with unequivocal negative emotional events associated with TTS. Interestingly, clinical presentation of patients with 'happy heart syndrome' was similar to those with the 'broken heart syndrome' including symptoms such as chest pain [89.5% (17/19) vs. 90.2% (412/457), P = 1.0]. Similarly, electrocardiographic parameters, laboratory findings, and 1-year outcome did not differ. However, in a post hoc analysis, a disproportionate higher prevalence of midventricular involvement was noted in 'happy hearts' compared with 'broken hearts' (35.0 vs. 16.3%, P = 0.030). CONCLUSION: Our data illustrate that TTS can be triggered by not only negative but also positive life events. While patient characteristics were similar between groups, the midventricular TTS type was more prevalent among the 'happy hearts' than among the 'broken hearts'. Presumably, despite their distinct nature, happy and sad life events may share similar final common emotional pathways, which can ultimately trigger TTS.

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CLINICAL RESEARCH
Heart failure/cardiomyopathy

Happy heart syndrome: role of positive emotional stress in takotsubo syndrome

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Aims Takotsubo syndrome (TTS) is typically provoked by negative stressors such as grief, anger, or fear leading to the popular term '*broken heart syndrome*'. However, the role of positive emotions triggering TTS remains unclear. The aim of the present study was to analyse the prevalence and characteristics of patients with TTS following pleasant events, which are distinct from the stressful or undesirable episodes commonly triggering TTS.

Methods and results Takotsubo syndrome patients with preceding pleasant events were compared to those with negative emotional triggers from the International Takotsubo Registry. Of 1750 TTS patients, we identified a total of 485 with a definite emotional trigger. Of these, 4.1% ($n = 20$) presented with pleasant preceding events and 95.9% ($n = 465$) with unequivocal negative emotional events associated with TTS. Interestingly, clinical presentation of patients with '*happy heart syndrome*' was similar to those with the '*broken heart syndrome*' including symptoms such as chest pain [89.5% (17/19) vs. 90.2% (412/457), $P = 1.0$]. Similarly, electrocardiographic parameters, laboratory findings, and 1-year outcome did not differ. However, in a *post hoc* analysis, a disproportionate higher prevalence of midventricular involvement was noted in '*happy hearts*' compared with '*broken hearts*' (35.0 vs. 16.3%, $P = 0.030$).

Conclusion Our data illustrate that TTS can be triggered by not only negative but also positive life events. While patient characteristics were similar between groups, the midventricular TTS type was more prevalent among the '*happy hearts*' than among the '*broken hearts*'. Presumably, despite their distinct nature, happy and sad life events may share similar final common emotional pathways, which can ultimately trigger TTS.

Keywords Takotsubo syndrome • Broken heart syndrome • Acute heart failure • Brain–heart connection

Introduction

Since the first description of takotsubo syndrome (TTS) in 1990,[1] evolving evidence suggests that TTS is typically precipitated by episodes of severe negative stress such as grief, anger, or fear.[2,3] These negative emotional triggers have led to the popular term '*broken heart syndrome*'.[4] It is well known that emotional distress may result in an overstimulation of the sympathetic nervous system and/or inappropriate parasympathetic withdrawal.[5] As a consequence, the resulting cardiovascular effects may lead to life-threatening arrhythmias,[6–8] TTS,[9] and even sudden cardiac death.[10,11] Wittstein *et al.* confirmed in a prospective study increased levels of circulating catecholamines in patients with TTS compared with those with Killip class III myocardial infarction,[12] suggesting that in TTS, stressful events indeed affect the cardiovascular system via an over-activation of the sympathetic neurohormonal axis.

On the other hand, the role of positive emotions in TTS is far less clear.[13,14] Positive emotions modulate the autonomic nervous system response to a similar degree as do negative emotions, which in turn alter heart rate, peripheral vascular resistance, and blood pressure.[5] However, conflicting results exist on the impact of positive emotions on cardiovascular disease. In the long-term, positive emotions have been associated with a reduced risk of cardiovascular disease,[15] while others have shown that they can also provoke acute coronary syndrome.[16] Of note, positive emotions can result not only in increased activation of the sympathetic nervous system but also in increased parasympathetic nervous system activity. Interestingly, the likelihood of experiencing a cardiovascular event on one's birthday is 27% higher than on any other day of the year.[17]

The aim of the present study was to analyse the prevalence and characteristics of TTS in patients after preceding pleasant rather than unpleasant events. Furthermore, we intend to raise awareness and compare this new conceptual entity of '*happy heart syndrome*' with '*broken heart syndrome*'.

Methods

Study population

The International Takotsubo Registry (InterTAK$_{Registry}$, www.takotsubo-registry.com) was established at the University Hospital Zurich in 2011. Patient recruitment and inclusion criteria have been recently published.[18]

In brief, data were collected from the leading hospital Zurich and 25 collaborating centres from 9 different countries (Austria, Finland, France, Germany, Italy, Poland, Switzerland, UK, and USA) between 2011 and 2014. Takotsubo syndrome was defined according to the modified Mayo Clinic Diagnostic Criteria.[18,19]

When eligibility for inclusion was uncertain, cases were reviewed by the core team at the leading centre to reach a consensus.[18]

The InterTAK$_{Registry}$ consists of currently 1750 patients, of which 485 presented with an emotional event leading to a TTS episode. The remaining patients had a physical, a combination of an emotional and physical, or no identifiable trigger.[18]

Patients with a preceding pleasant emotional event prior to TTS were classified as '*happy hearts*', while patients with a preceding negative emotional event were categorized as '*broken hearts*'.

The complete medical records of the cardiovascular history preceding the episode of TTS were reviewed in detail and documented as well as the acute index TTS event by standardized forms. Data were collected on clinical presentation, precipitating factors, cardiovascular risk factors, electrocardiographic findings, cardiac biomarkers, inflammatory markers, medications, demographics, angiographic and echocardiographic parameters, in-hospital complications, acute cardiac care. Furthermore, follow-up was obtained through telephone interviews, clinical visits or medical records.

Wall motion pattern was classified as apical ballooning (i.e. typical) or midventricular, basal, or focal type (all designated as atypical), respectively.[18] Left ventricular ejection fraction (LVEF) and left ventricular end-diastolic pressure (LVEDP) were evaluated if assessed. The registry adhered to the requirements of the respective local ethics committee (ClinicalTrials.gov number: NCT01947621).

Statistical analysis

Continuous data are given as mean ± SD, laboratory values are given as median (interquartile range), and categorical variables are expressed as numbers and percentages. Differences between groups were tested using the Pearson χ^2 test or the Fisher's exact test for nominal data, or Mann–Whitney *U* test for continuous data. A *post hoc* analysis was performed for comparison between TTS types among '*happy*' and '*broken*' hearts. One-year survival analysis was performed using the Kaplan–Meier method, and the *P*-value was calculated with the log-rank test.

Statistical analyses were performed using IBM SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as two-sided $P < 0.05$. Graph was compiled with Prism 6 (GraphPad, La Jolla, CA, USA).

Results

Patient characteristics

Of 485 patients with an emotional event, 4.1% ($n = 20$) were identified to have '*happy heart syndrome*', while the majority of patients (95.9%, $n = 465$) had '*broken heart syndrome*'.

Women were over-represented ($P < 0.001$) without differences between both groups ['*happy hearts*' 95.0% (19/20) and '*broken hearts*' 94.6% (440/465), $P = 1.0$]. The mean age of patients was 71.4 ± 11.2 years in '*happy hearts*' and 65.0 ± 12.5 years in '*broken hearts*' ($P = 0.026$). Specific joyful emotional events associated with the onset of TTS are shown in *Table 1*, and negative emotional events are presented in *Table 2*.

Analysis of the socioeconomic status showed that among '*happy heart*' patients 20.0% (3/15) were living alone, while 80.0% (12/15) had a partner. This was similar to '*broken heart*' patients in which 29.3% (92/314) lived alone and 70.7% (222/314) were living with someone ($P = 0.67$). Of note, the majority of patients was unemployed or retired at the time of the index episode in both '*happy heart syndrome*' [92.3% (12/13)] and '*broken heart syndrome*' [59.7% (187/313)] ($P = 0.018$). Characteristics of '*happy hearts*' and '*broken hearts*' are summarized in *Table 3*.

Table 1 Happy heart events ($n = 20$)

Patient 1	Birthday party
Patient 2	Son's wedding
Patient 3	Meeting after 50 years with friends from high school
Patient 4	Preparing 50th wedding anniversary (pleasant anticipation)
Patient 5	Positive job interview
Patient 6	Wedding
Patient 7	Favourite driver won race car competition
Patient 8	Becoming grandmother
Patient 9	Surprise farewell celebration
Patient 10	Son's company opening
Patient 11	Favourite rugby team won game
Patient 12	Emotional speaking during a friend's birthday
Patient 13	Celebrating 80th birthday
Patient 14	Winning several jackpots at the casino
Patient 15	Celebration of normal PET-CT scan
Patient 16	Visiting opera with her family
Patient 17	Family party
Patient 18	Unexpected visit from favourite nephew
Patient 19	Grandchildren visiting from London (abroad)
Patient 20	Becoming great grandmother

Symptoms at presentation

Chief complaints upon admission included chest pain in 89.5% (17/19) and dyspnoea in 26.3% (5/19) of the documented '*happy heart*' patients. These findings were similar for '*broken hearts*' in which chest pain was present in 90.2% (412/457) ($P = 1.0$) and dyspnoea in 44.6% (200/448) ($P = 0.12$).

There were no significant differences in symptoms onset to hospitalization within the first 24 h between '*happy hearts*' [100% (20/20)] and '*broken hearts*' [84.9% (383/451)] ($P = 0.054$).

Electrocardiogram

Electrocardiogram on admission showed the following abnormalities for '*happy heart syndrome*' vs. '*broken heart syndrome*': ST-segment elevation was present in 50.0% (10/20) vs. 44.5% (193/434) ($P = 0.63$), ST-segment depression occurred in 15.0% (3/20) vs. 5.5% (24/434) ($P = 0.08$), T-wave inversion was present in 45.0% (9/20) vs. 40.3% (175/434) ($P = 0.68$), and left bundle branch block was observed in 5.0% (1/20) vs. 5.1% (22/434) ($P = 1.0$).

Most patients [95.0% (19/20) vs. 93.8% (407/434), $P = 1.0$] were in sinus rhythm, while 5.0% (1/20) vs. 5.5% (24/434) ($P = 1.0$) presented with atrial fibrillation. Atrioventricular block was found in 15.0% (3/20) vs. 3.9% (17/434) ($P = 0.052$).

Vital signs and haemodynamics

Systolic blood pressure on admission averaged 135.2 ± 45.2 mmHg in '*happy hearts*' vs. 130.6 ± 26.2 mmHg in '*broken hearts*' ($P = 0.47$) and diastolic blood pressure 79.5 ± 19.8 mmHg vs. 76.6 ± 15.4 mmHg ($P = 0.42$), while mean heart rate was 86.2 ± 17.4 b.p.m. vs. 85.3 ± 19.3 b.p.m. ($P = 0.85$).

Mean LVEDP was not different between the two groups (22.8 ± 11.0 mmHg vs. 21.1 ± 7.6 mmHg, $P = 0.47$). Mean LVEF on admission averaged 40.2 ± 9.4% in '*happy hearts*' vs. 42.6 ± 11.0% in '*broken hearts*' ($P = 0.36$) (*Table 3*).

Laboratory values

Admission and peak laboratory values did not significantly differ between '*happy hearts*' and '*broken hearts*' (*Table 3*).

Takotsubo type

Patients with a '*happy heart syndrome*' showed an apical ballooning pattern in 65.0% (13/20). The midventricular TTS type was noted in 35.0% (7/20). None of the patients presented with a basal or focal TTS type. Patients with '*broken hearts*' had apical ballooning in 79.8% (371/465) and midventricular TTS in 16.3% (76/465). The basal TTS type was present in 1.9% (9/465) and the focal type in 1.9% (9/465).

The overall distribution of TTS types between '*happy hearts*' and '*broken hearts*' was not significantly different ($P = 0.21$). In a *post hoc* comparison, however, a disproportionate higher prevalence of midventricular involvement was noted in '*happy hearts*' compared with '*broken hearts*' (35.0 vs. 16.3%, $P = 0.030$) (*Figure 1*).

Table 2 Broken heart events (emotional, $n = 465$)

1. Grief/loss ($n = 107$)	
Death of spouse	6.5% (30/465)
Attending a funeral	3.4% (16/465)
Death in the family (no more details)	3.2% (15/465)
Death of mother/father	2.8% (13/465)
Death of a child	1.9% (9/465)
Death of brother/sister	1.7% (8/465)
Death of a friend	1.5% (7/465)
Close person moving	1.1% (5/465)
Loss of home	0.4% (2/465)
Grief/loss (no details)	0.4% (2/465)
2. Panic/fear/anxiety ($n = 107$)	
Illness of a close person	6.5% (30/465)
Accident (car/ship/plane)	2.4% (11/465)
Fall	2.2% (10/465)
Fire/flooding (house damaged)	1.5% (7/465)
Robbery/burglary	1.3% (6/465)
Anxiety (no details)	1.3% (6/465)
Feared of own hospitalization	1.1% (5/465)
Fear of surgery/medical intervention	1.1% (5/465)
Worried about own illness	0.9% (4/465)
Panic attack	0.9% (4/465)
Being threatened by someone	0.9% (4/465)
Court date	0.6% (3/465)
Caught by the police	0.4% (2/465)
Animal/pet hurt	0.4% (2/465)
Nightmare	0.2% (1/465)
Obese patient stuck in bathtub	0.2% (1/465)
Loneliness	0.2% (1/465)
Frightened of difficult ski slope	0.2% (1/465)
Frightened of a dog	0.2% (1/465)
Airplane crash in flight simulator	0.2% (1/465)
Investing in stock market	0.2% (1/465)
Locked herself out	0.2% (1/465)
3. Interpersonal conflict ($n = 78$)	
Family problems	6.2% (29/465)
Problems with children	3.2% (15/465)
Depression	2.4% (11/465)
Relationship problems/divorce	0.6% (3/465)
Burdening/stressful phone call	0.6% (3/465)
Suicide attempt	0.6% (3/465)
Taking care of a person	0.6% (3/465)
Drug abuse	0.4% (2/465)
Father disinherited the patient	0.2% (1/465)
Problems with tenants	0.2% (1/465)
Problems with physician	0.2% (1/465)
Abused by a relative	0.2% (1/465)
Spoke about difficult childhood for the first time	0.2% (1/465)
Psychotic neighbour	0.2% (1/465)
Supposed to meet ex-partner on vacation	0.2% (1/465)
Discussion with priest at a church meeting	0.2% (1/465)
Disappointed by a friend	0.2% (1/465)
4. Anger/frustration ($n = 77$)	
Argument (no more details)	5.2% (24/465)
Argument with family	3.7% (17/465)
Argument with spouse	2.2% (10/465)
Argument with neighbour	1.3% (6/465)
Argument at work	0.9% (4/465)
Angry with child	0.9% (4/465)
Argument with employer	0.4% (2/465)
Argument with friend	0.4% (2/465)
Argument with brother/sister	0.4% (2/465)
Angry, lost purse	0.2% (1/465)
Angry, stuck in a traffic congestion	0.2% (1/465)
Angry, old tree being logged	0.2% (1/465)
Frustrated, favourite football team lost game	0.2% (1/465)
Frustrated, car was stolen	0.2% (1/465)
Argument requiring police involvement	0.2% (1/465)
5. Financial/employment problems ($n = 37$)	
Stress at work	6.7% (31/465)
Retirement	0.6% (3/465)
Financial problems	0.4% (2/465)
Debt	0.2% (1/465)
6. Others ($n = 59$)	
No details	12.7% (59/465)

Medication

Upon presentation, a minority of patients had previously taken cardiovascular medications on a regular basis. Medication on admission in the '*happy heart*' and '*broken heart*' groups included angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [33.3% (5/15) vs. 38.3% (153/400), $P = 0.70$], β-blockers [33.3% (5/15) vs. 34.8% (139/400), $P = 0.91$], statins [20.0% (3/15) vs. 18.0% (70/388), $P = 0.74$], and aspirin [33.3% (5/15) vs. 34.8% (135/388), $P = 0.91$] (*Table 3*).

Clinical course and outcomes

Acute cardiac care was similar in both '*happy heart*' and '*broken heart*' groups ($P = 0.67$). In the '*happy heart*' patient population, 5.0% (1/20) received intra-aortic balloon pump compared with 1.3% (6/464) ($P = 0.26$) in the '*broken hearts*'. There were no statistically significant differences in mechanical ventilation [10.0% (2/20) vs. 4.1% (19/464), $P = 0.21$] and catecholamine administration [5.0% (1/20) vs. 5.0% (23/464), $P = 1.0$].

Among the in-hospital complications, death occurred in none of the patients with '*happy hearts*' while 1.1% (5/465) of patients with '*broken heart*' died during hospitalization ($P = 1.0$). Cardiogenic shock occurred in none of '*happy hearts*' compared with 3.7% (17/459) in '*broken hearts*' ($P = 1.0$). Ventricular or septal rupture was identified in none of the groups. Ventricular tachycardia occurred in none of '*happy hearts*' vs. 2.2% (10/459) among patients

Table 3 Comparison of patients with happy and broken heart syndrome

Characteristics	Happy heart $n = 20$	Broken heart $n = 465$	*P*-value
Demographics			
Female sex (%) (*n*/total *n*)	95.0 (19/20)	94.6 (440/465)	1.0[a]
Age (year)	71.4 ± 11.2 ($n = 20$)	65.0 ± 12.5 ($n = 465$)	0.026
Body mass index (kg/m^2)	23.4 ± 3.0 ($n = 16$)	25.1 ± 4.9 ($n = 380$)	0.18
Vital signs			
Heart rate (b.p.m.)	86.2 ± 17.4 ($n = 19$)	85.3 ± 19.3 ($n = 397$)	0.85
Systolic blood pressure (mmHg)	135.2 ± 45.2 ($n = 19$)	130.6 ± 26.2 ($n = 402$)	0.47
Diastolic blood pressure (mmHg)	79.5 ± 19.8 ($n = 18$)	76.6 ± 15.4 ($n = 397$)	0.42
Haemodynamics			
Left ventricular ejection fraction (%)[b]	40.2 ± 9.4 ($n = 18$)	42.6 ± 11.0 ($n = 434$)	0.36
Left ventricular end-diastolic pressure (mmHg)	22.8 ± 11.0 ($n = 11$)	21.1 ± 7.6 ($n = 270$)	0.47
Laboratory values			
Troponin on admission, factor increase in ULN[c]	5.1 (1.7–13.3) $n = 16$	8.5 (3.0–22.0) $n = 396$	0.19
Troponin maximum, factor increase in ULN[c]	11.3 (2.4–17.5) $n = 16$	12.9 (4.7–34.0) $n = 403$	0.20
Creatine kinase on admission, factor increase in ULN	0.8 (0.5–2.3) $n = 13$	0.9 (0.6–1.4) $n = 341$	0.08
Creatine kinase maximum, factor increase in ULN	0.9 (0.6–2.2) $n = 13$	1.1 (0.7–1.7) $n = 341$	0.86
C-reactive protein on admission (mg/L)	2.8 (2.0–3.1) $n = 11$	3.0 (1.0–7.2) $n = 336$	0.86
C-reactive protein maximum (mg/L)	11.4 (2.8–23.5) $n = 12$	5.6 (2.2–15.8) $n = 354$	0.45
WBC on admission (10^3/μL)	8.8 (7.7–12.0) $n = 18$	9.3 (7.2–11.4) $n = 385$	0.91
WBC maximum (10^3/μL)	9.5 (7.8–12.4) $n = 19$	9.8 (7.7–11.9) $n = 401$	0.98
ECG on admission (%) (*n*/total *n*)			
Sinus rhythm	95.0 (19/20)	93.8 (407/434)	1.0[a]
Atrial fibrillation	5.0 (1/20)	5.5 (24/434)	1.0[a]
AV block	15.0 (3/20)	3.9 (17/434)	0.052[a]
ST-segment elevation	50.0 (10/20)	44.5 (193/434)	0.63
ST-segment depression	15.0 (3/20)	5.5 (24/434)	0.08[a]
T-wave inversion	45.0 (9/20)	40.3 (175/434)	0.68
Left bundle branch block	5.0 (1/20)	5.1 (22/434)	1.0[a]
Cardiovascular risk factors (%) (*n*/total *n*)			
Hypertension	35.0 (7/20)	62.4 (286/458)	0.014
Diabetes mellitus	0.0 (0/20)	10.7 (49/456)	0.25[a]
Current smoking	15.0 (3/20)	18.4 (83/451)	0.56[a]
Hypercholesterolaemia	25.0 (5/20)	32.5 (149/458)	0.48
Medication on admission (%) (*n*/total *n*)			
ACE inhibitor or ARB	33.3 (5/15)	38.3 (153/400)	0.70
β-Blocker	33.3 (5/15)	34.8 (139/400)	0.91
Calcium-channel antagonist	0.0 (0/15)	4.9 (19/388)	1.0[a]
Statin	20.0 (3/15)	18.0 (70/388)	0.74[a]
Aspirin	33.3 (5/15)	34.8 (135/388)	0.91
Antidepressant	16.7 (3/18)	9.8 (38/388)	0.19[a]

Values are presented as % (*n*/total *n*), means ± SD, or median (interquartile range).
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AV block, atrioventricular block; ECG, electrocardiogram; ULN, upper limit of the normal range; WBC, white blood cell count.
[a]Fisher's exact test.
[b]Left ventricular ejection fraction was obtained either during catheterization or echocardiography. If both results were present, data that were obtained during catheterization were used.
[c]Included are upper limits of the normal range for troponin T, high-sensitive troponin T, and troponin I.

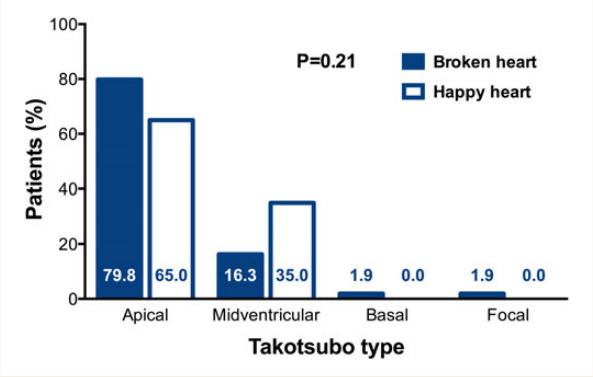

Figure 1 Overall distribution of takotsubo types in '*happy heart syndrome*' vs. '*broken heart syndrome*' ($P = 0.21$). *Post hoc P*-values for comparison within takotsubo types showed a significantly higher prevalence of the midventricular takotsubo syndrome type in patients with '*happy heart*' vs. '*broken heart*' ($P = 0.030$), while no significant differences were seen in apical ($P = 0.15$), basal ($P = 1.0$), or focal ($P = 1.0$) takotsubo syndrome types.

with '*broken hearts*' ($P = 1.0$). Ventricular thrombus was present in 5.0% (1/20) of the '*happy hearts*' vs. 1.1% (5/459) in '*broken hearts*' ($P = 0.23$). New atrial fibrillation occurred in none of the '*happy heart*' patients. Patients with '*broken heart syndrome*' presented with new atrial fibrillation in 3.7% (17/459) ($P = 1.0$).

There was no statistical significance for the respective complications between the two groups of '*happy hearts*' and '*broken hearts*'.

One-year survival was comparable between '*happy hearts*' and '*broken hearts*' (100% vs. 97.6 $\pm$ 0.9%, $P = 0.52$).

Discussion

Here, for the first time, we present a systematic analysis of patients diagnosed with TTS after joyful or socially desirable events, contrary to the well-established literature. Our data are derived from the largest study on TTS worldwide examining a plethora of characteristics of 1750 TTS cases, based on the most comprehensive available data thus far in the literature.[18] Interestingly, symptoms such as chest pain and dyspnoea as well as the baseline characteristics and clinical findings upon admission including cardiovascular risk factors and laboratory findings were similar between those with '*happy heart syndrome*' and '*broken heart syndrome*', respectively, regardless of the nature of the triggering event.

It is now recognized that TTS predominantly affects postmenopausal women[20] and is often triggered by an emotional or a physical stressor.[21] Thus far, large numbers of TTS cases have been reported after adverse emotional events, e.g. the death of a beloved one.[21] Consequently, TTS is also widely known as the '*broken heart syndrome*'.[22]

In our analysis, the distribution of various TTS phenotypes among patients presenting with '*broken heart*' was similar to that of Eitel *et al.*[23] Interestingly, we found a higher prevalence of the midventricular takotsubo type in the '*happy heart*' group.

Our study characterizes a novel clinical presentation of TTS and might indeed provide important insights into the brain–heart interaction, which most likely contributes to the pathophysiology of TTS. An early systematic study established a social readjustment rating scale, which included multiple life events and the subsequent analysis of health consequences, in particular time of onset of illness.[24] Among the precipitating factors to be rated, several desirable events, including marriage, marital reconciliation with one's mate, outstanding personal achievements, vacations, and holidays, were included. Unfortunately, this early inclusion of positive events, perhaps motivated by clinical intuition, did not prevent subsequent clinical research from unilaterally focussing on negative events as triggers for TTS. For the first time in decades, now the findings by Holmes and Rahe have been eventually confirmed.[24] Our analysis corroborates the link between positive emotional experience and TTS. This is a novel and substantial paradigm shift from the commonly accepted inciting events involved in developing TTS.

It is now generally accepted that one's emotional state plays a role in the overall health of the individual. Therefore, our findings may broaden the whole spectrum of the nature of this multifaceted disease. However, the exact consequences of psychological states and their manifestations in various clinical syndromes such as TTS have not been thoroughly explored. As such, the exact molecular pathways and functional anatomy of the central nervous system involved in emotional processing, which are likely to be responsible for their systemic effects, remain poorly understood.

Similarly, our knowledge regarding the involvement of the central nervous system in the pathogenesis of cardiovascular disease remains insufficient. However, ample epidemiological studies have demonstrated that the central nervous system indeed plays a prominent role in cardiovascular disease. Earlier imaging studies have revealed activation of specific cortical and subcortical areas of the brain associated with distinct emotional processing[25–27] such as extended activation in both temporal lobes during certain emotions including happiness, sadness, and fear, but not during disgust or anger.[28] Subcortical structures including the amygdala, hippocampus, and basal ganglia have also been implicated in emotional processing. The amygdala is not only associated with negative emotions but has been recently also implicated in the processing of pleasant emotions such as happiness.

Given that the prevalence of the '*happy heart syndrome*' is only 1.1% among all TTS cases, '*happy*' events may necessitate more potent stimuli to induce a substantial emotional response than negative emotions. Perhaps the threshold to influence the cardiovascular system is higher when happy events are processed. Alternatively, this might be simply explained by the propensity of certain individuals to emotional events. At this point, given the lack of data, we cannot speculate if individuals with preceding happy events developing TTS would have suffered similar consequence with preceding negative emotions. Therefore, it is plausible that the individual's brain biochemistry, processing, and response to emotions are distinct and can explain this observed phenomenon.

Limitations

Patients with '*happy heart syndrome*' had a higher prevalence of the midventricular TTS type than those with '*broken heart syndrome*'. Although this observation is interesting and novel, it is hypothesis generating and based on a small subset of patients, which poses a limitation in explaining the precise mechanism involved. Therefore,

these findings merit further large-scale investigations, particularly in patients with TTS and preceding pleasant emotional triggers.

Since the study is of observational nature, some values were missing despite extensive chart review. The small number of '*happy hearts*' may have resulted in statistical non-significance of clinically relevant findings. Nonetheless, retrospective data analysis is particularly valuable in understudied diseases, such as TTS with a low incidence where the pathophysiology continues to remain elusive.

Conclusion

This novel observation of pleasant emotional stressors in triggering TTS may lead to a paradigm shift in clinical practice by raising awareness among physicians. While the role of negative life events such as anger, grief, or physical stressors in provoking TTS is acknowledged, the association between positive emotions and TTS is not commonly recognized. Therefore, our findings further expose the multifaceted nature of this disease and broaden the spectrum of triggers associated with this fascinating disease.

Furthermore, we believe that TTS is a classic example of a complex intertwined feedback loop encompassing psychological and/or physical stimuli within the brain that subsequently impact the cardiovascular system. Perhaps, both happy and sad life events, while inherently distinct in nature, share a final common pathway in the central nervous system processing and output, which can ultimately trigger TTS. Clearly, future research is warranted to investigate this possibility and delineate the exact mechanisms underlying both '*broken*' and '*happy*' heart variants of TTS.

Authors' contributions

B.S., J.D., V.L.C., and L.C.N. performed statistical analysis. C.T. and J.R.G. handled funding and supervision. J.D., D.R.B., and J.R.G. acquired the data. C.T. and J.R.G. conceived and designed the research. C.T., J.R.G., and A.S. drafted the manuscript. T.F.L., L.C.N., F.R., and F.S. made critical revision of the manuscript for key intellectual content.

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